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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,980	04/03/2007	Roland Reiner	067802-5008	7700

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,980	REINER ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23 and 27-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 27-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 11/11/2010 has been received, entered and carefully considered. The following information has been made of record in the instant amendment:

1. Claims 1-22 and 24-26 have been canceled.

2. Claim 23 has been amended to recite "fully-crosslinked".

3. Remarks drawn to rejections under 35 USC 103(a).

Claims 23 and 27-49 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 23-31, 36, 38-40 and 42-46 under 35 U.S.C. 103(a) as being unpatentable over Marler et al (Plast. Reconstr. Surg., 2000, 105, 2049-2058; of record) in view of Bent et al (Neurourology and Urodynamics, 2001, 20, 157-165; of record), Kuo et al (Biomaterials 2001, 22, 511-521, of record) and Vanderhoff et al (WO 96/39464; of record) is being maintained for reasons of record and is reiterated below.

Marler et al teach tissue augmentation (increasing shape and volume) via subcutaneous injection of a composition comprising an alginate, into a rat (page 2049 Abstract, first, second and last paragraphs; page 2050, right column, first full paragraph). The composition comprised alginate covalently bonded to RGD, a cell adhesion peptide. The alginates were used in cell culture medium to provide nutrients and phosphate buffered saline (page 2050, right col., last paragraph; part of limitations of claim 38 and claim 39: for carrier). The alginate was reconstituted as a 2% solution and gelled via crosslinking with calcium ions (page 2051, left col., first full paragraph). The alginate solutions with or without the cells were allowed to gel in vivo, after injection of a mixture of alginate, cell and calcium ions (page 2051, right column, first paragraph). Marler also discloses that calcium alginate was best able to support a specific soft tissue construct when it was crosslinked after injection (page 2056, second full paragraph; limitation of claim 46).

Bent et al teach the treatment of incontinence by injection of alginate solution crosslinked (gelled) with calcium ions and containing chrondrocytes, into the sphincter muscle (page 157, abstract through page 158, middle; limitation of claims 29-31).

However, Marler et al and Bent et al do not teach the molecular weight of the alginate prior to crosslinking.

Kuo et al teach the use of calcium alginate gels for tissue engineering. Alginate gel beads are formed by slow gelling using calcium carbonate/D-glucono-δ-lactone combination to form structurally uniform gels. Cells are incorporated into the gels and combination acts as a time-delayed release of calcium ions (page 512, left column first paragraph; page 513, left column, section 2.6; limitations of claim 23, 35, 38, 47). Kuo discloses that in their study alginates used had molecular weights of about 373 and 463 kD and that they had better mechanical properties (molecular weight limitation of claim 23). This means that alginates having high molecular weights in the range taught by Kuo or even higher are suitable for making gels that are stronger and suitable for biomedical applications. According to Kuo ionic crosslinking is preferable compared to covalent crosslinking since covalent crosslinking agents are toxic. Moreover gelling with ionic crosslinking agents like calcium gives gels that are homogeneous (page 517, left col., paragraph below Fig. 6; right col., middle paragraph).

Vanderhoff et al teach polymer particles of about 150 micrometers for use in soft tissue augmentation (page 4, line 20 through page 5, line 4; limitations of claims 23 and 40). The injectable particles can also contain encapsulated drugs and medications (page 5, lines 5-9; lines 25-31; page 7, lines 6-35; part of the limitations of claim 38). The water soluble polymers can be polysaccharides (page 8, lines 32-34). One of the desirable polymers is sodium alginate

(limitation of claim 32), since it is biocompatible, biodegradable, and non immunogenic and in the form of microspheres is a good candidate as carrier of drugs (page 9, lines 7-20). Several types of crosslinking agents can also be used depending upon the polymer used and can be readily determined by one of skill in the art (page 9, lines 21-35). For crosslinking of the microparticles, pH can be adjusted to adjust the rate of crosslinking (page 10, lines 20-21). Even though Vanderhoff's teaching is drawn to a process for producing microparticles, he suggests the use of such particles also for tissue augmentation. One of skill in the art will use such microparticles of alginate for tissue augmentation as taught by Marler, Bent and Kuo. Even though Vanderhoff discloses that ionic crosslinking may be broken by chelating agents, his alternative of using covalent crosslinking agents is not actually preferable since covalent crosslinking agents are taught to be toxic by Kuo (as above). This would persuade one of ordinary skill in the art to use ionic crosslinking. Gels having such crosslinks have been made and used as seen from Marler, Bent and Kuo.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use alginates, crosslinked with calcium and sodium and uncrosslinked, in the form of microspheres, for increasing the volume of tissue in a subject, as instantly claimed since the use of such is taught using analogous alginates (having different molecular weight range) for the same purpose.

One of skill in the art would be motivated to use alginates in the method as instantly claimed since Marler teaches that the use of alginates offers additional advantages like chemical modification to induce desirable properties, is readily available and has been approved by FDA for use in human patients (Marler, page 2054, right column, first and second paragraphs).

According to Vanderhoff, one of the desirable polymers is sodium alginate, since it is biocompatible and non immunogenic and in the form of microspheres is a good candidate as carrier of drugs (page 9, lines 7-20). According to Kuo, alginates having high molecular weights form stable gels. With so many advantages, one of skill in the art would prefer to use alginate over other polymers suggested in the prior art.

The rejection of Claims 32-35, 37, 41 and 47-49 under 35 U.S.C. 103(a) as being unpatentable over Marler et al (Plast. Reconstr. Surg., 2000, 105, 2049-2058; of record) in view of Kuo et al (Biomaterials 2001, 22, 511-521, of record), Vanderhoff et al (WO 96/39464; of record), Grandolfo et al (Calcified Tissue International, 1993, 52, 42-48, of record) and Wong (Alginates in Tissue Engineering, 2003, 238, 77-86, Abstract; of record) is being maintained for reasons of record and is reiterated below.

The teachings of Marler, Kuo and Vanderhoff et al is as above. Marler, Kuo and Vanderhoff do not teach the use of citrate, EDTA, barium ions and additional ions as recited in the instant claims.

Kuo et al teach the use of calcium alginate gels for tissue engineering. Alginate gel beads are formed by slow gelling using calcium carbonate/D-glucono-δ-lactone combination to form structurally uniform gels. Cells are incorporated into the gels and combination acts as a time-delayed release of calcium ions (page 512, left column first paragraph; page 513, left column, section 2.6; limitations of claim 47).

Grandolfo et al teach that calcium alginate gels can be used to trap cells which can be released using citrate or EDTA (page 42, right col., first full paragraph; part of the limitations of

claim 48). This means that other than cells, encapsulated drugs and medications can be slowly released at sites where the gels are incorporated.

Wong teaches the use of ions like calcium and barium to make gels of alginate for medical applications (abstract; limitations of claims 33-34).

One of skill in the art would also prefer to use EDTA or gluconolactone since both are sequestering agents and can also aid in slowly releasing encapsulated agents like cells and drugs. The use of citrate is also logical since it is a component of the well known citrate buffer used for adjusting pH and also helps in the release of encapsulated agents. Also in line with the teaching of Vanderhoff regarding the adjustment of pH for adjusting the rate of crosslinking, the use of the biocompatible citrate is preferable (Vanderhoff page 10, lines 20-21). Since calcium, sodium and barium ions are seen to be used in the prior art the use of a combination of these ions for crosslinking the alginate is obvious for the advantages as explained above. It is well within the skill level of the artisan to adjust the percentages of the agents, the size of the microparticle and the molecular weight of the alginate in order to obtain maximum beneficial effects.

Response to Applicants' Arguments

Applicants have traversed both the rejections above by arguing that:

1. Marler teaches that a pre-gelled alginate injection retains only about 30% of its volume 8 weeks post injection and thus teaches away from pre-gelling of alginate.

2. Bent's pre-gelled alginate degrades to the point that the remaining cells then secrete a matrix which maintains the volume of the original injection (page 158, 2nd full para).

Accordingly one of ordinary skill in the art would be deterred from using bent's alginate to increase tissue volume.

3. Vanderhoff emphasizes that covalent crosslinking is preferred.

4. Kuo teaches a slow crosslinking system. His gel, due to slow crosslinking system, essentially contains un-crosslinked alginate particles. This is a teaching away from fully crosslinked alginates.

5. Applicants have found that fully ionic crosslinked alginates with molecular weight range between 100kDa and 1200kDa showed long term stability and which maintains its volume of up to 90% even after 6 months of implantation (Figures 1-3 in Appendix provided). They were also biocompatible.

Applicants' arguments and Figures 1-3 in Appendix have been considered but are not found to be persuasive.

Marler teaches that a volume of 88% could be maintained over eight weeks using calcium alginate for tissue augmentation (page 2056, left col., second full paragraph). Applicants claim 90%, which is very close. According to Marler crosslinking of alginate gel is known to be done before and after injection of the alginate.

Bent teaches (see conclusion at page 164) that the use of chondrocytes suspended in calcium alginate gel is safe and effective (page 162, Discussion) and patients remained dry for 12 months after injection of the gel in incontinence tests. This in combination with Marler's teaching will not deter one of ordinary skill in the art from using fully crosslinked alginate gel as instantly claimed.

Vanderhoff teaches that covalent crosslinking is preferred. Even though Vanderhoff discloses that ionic crosslinking may be broken by chelating agents, his alternative of using covalent crosslinking agents is not actually preferable since covalent crosslinking agents are taught to be toxic by Kuo (as above). This would persuade one of ordinary skill in the art to use ionic crosslinking. Gels having such crosslinks have been made and used as seen from Marler, Bent and Kuo. Hence one of ordinary skill in the art would prefer to use ionic crosslinking given the toxicity of covalent crosslinking agents. Moreover, Vanderhoff does not teach that ionic crosslinking should not be used at all.

Kuo may have used slow crosslinking systems. But he discloses that in their study alginates used had molecular weights of about 373 and 463 kD and that they had better mechanical properties (molecular weight limitation of claim 23). This means that alginates having high molecular weights in the range taught by Kuo or even higher are suitable for making gels that are stronger and suitable for biomedical applications. One of ordinary skill in the art would expect such stronger gels to not degrade rapidly, especially in view of Marler's teaching of retention of volume of 88% even after 8 weeks.

Applicants argue that they have found that fully ionic crosslinked alginates with molecular weight range between 100kDa and 1200kDa showed long term stability and which maintains its volume of up to 90% even after 6 months of implantation (Figures 1-3 in Appendix provided). They were also biocompatible. The claimed molecular weight alginate is taught in the prior art (Kuo). Long term stability with retention of 88% volume using calcium alginate is taught by Marler. Vanderhoff teaches that alginate gels are biocompatible. Therefore one of ordinary skill in the art would expect biocompatibility, stability and retention of volume even

longer based on the teaching of Marler. There is reasonable expectation of success. Applicants claim of superior properties that are unexpected are not really unexpected. Such superior properties is seen for alginate gels according to the prior art.

Conclusion

Claims 23 and 27-49 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623